SHORT COMMUNICATION

Reactivation histoplasmosis after treatment with anti-tumor necrosis factor α in a patient from a nonendemic area

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Summary Histoplasma capsulatum (HC) is a thermally dimorphic ascomycete that is a significant cause of respiratory infections (> 80%) in endemic areas (Midwest and southeast USA), but infections are rare in non-endemic areas. Most primary HC infections are subclinical or self-limited. While reactivation Histoplasmosis has been reported in the setting of immunosuppression, it remains unclear whether remote primary latent infection represents risk of endogenous reactivation after anti-tumor necrosis factor (TNF)-α therapy [Yusuf H, Craig GT, Allan D. Disseminated histoplasmosis presenting with oral lesions—report of a case. Br J Oral Surg 1979;16(3):234–40; Catanzaro A, Spitler LE, Campbell GD, Moser KM. Transfer factor therapy for histoplasmosis in a patient with Hodgkin’s disease. Arch Intern Med 1981;141(4):533–7; Fredricks DN, Rojanasthien N, Jacobson MA. AIDS-related disseminated histoplasmosis in San Francisco, California. West J Med 1997;167(5):315–21]. We report a case of a patient who developed reactivation Histoplasmosis after receiving anti-TNF-α. To our knowledge, this is the first clear report of reactivation of “latent” Histoplasmosis after anti-TNF-α therapy.

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Case report

Our patient is a 40-year old man with a history of Crohn’s disease being treated with infliximab (anti-TNF-α therapy) and intermittent prednisone for approximately one year. He presented with cough minimally productive of clear to whitish sputum, shortness of breath, a 10-lb weight loss over the previous 6 weeks, fevers and night sweats. He had traveled to an area endemic for Histoplasma capsulatum (HC) 5 years prior to presentation, but he denied travel outside of California in the last 5 years. On exam, he was in no respiratory distress but had bilateral inspiratory crackles at both lung bases.

Abbreviations: HC, Histoplasma capsulatum; IL, Interleukin; TNF, tumor necrosis factor

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bases. Laboratory studies revealed normal complete blood count and liver function tests. Chest X-ray demonstrated diffuse alveolar infiltrates bilaterally. Transbronchial lung biopsy specimen showed well-formed granuloma consisting of nodules of epithelioid histiocytes and lymphocytes without evidence of multinucleated giant cells, necrosis or vasculitis. Bronchoalveolar lavage grew HC but was negative for acid-fast bacilli, Pneumocystis carinii, cryptococcus, and coccidiomycosis.

Anti-TNF-α therapy was held and the patient responded well to itraconazole therapy.1–3

Discussion

HC is a soil fungus endogenous to the southeastern US, mid-Atlantic States, and the Ohio and Mississippi River Valleys.4 Primary infection with HC is usually subclinical or self-limited but may present as a fulminant infection in immunocompromised patients. Animal models clearly demonstrate the protective role for TNF-α in primary and secondary infection, but the role of TNF-α in reactivation of Histoplasmosis is not clear.5–7 Two previous reports of Histoplasmosis in patients receiving either infliximab or etanercept occurred in patients living in endemic regions.6,9 While the time course of Histoplasmosis after anti-TNF-α suggested reactivation,10 these patients could have experienced reinfection. Mouse models have demonstrated that anti-TNF increases the risk for reinfection.6 Our patient is unique in that he had previously traveled in an endemic area for HC, but denied travel outside California for 5 years. Thus our case represents the clearest evidence that TNF-α is important in preventing reactivation of Histoplasmosis.

The T-cell immune response is divided into a TH1 response that generates interferon (IFN)-γ and TNF-α and a TH2 response that generates IL-4 and IL-10. Both IL-4 and IL-10 have been investigated for their protective role in Crohn’s disease.11,12 Presumably anti-TNF-α exerts its beneficial effect on Crohn’s disease by decreasing TNF-α levels directly or by shifting the immune response from a TH1 to a TH2 predominance. Increased levels of IL-4 and IL-10 increase the risk for primary and secondary infection with HC and may contribute to increased risk for reactivation Histoplasmosis. It has been demonstrated previously that TNF-α plays a critical role in mediating a protective response to secondary HC infections in the absence of INF-γ.8 Taken together, these data suggest that T-cell derived TNF-α (and INF-γ) may play a critical role in inhibiting (or eradicating) HC infection over time after the primary exposure, reducing the risk of reactivation.

Increased use of TNF antagonists have been associated with increased frequency of some granulomatous infections in patients treated with these agents.10 While reactivation tuberculosis following TNF blockade has been widely reported, reactivating other infections such as coccidiomycosis have not been reported. Our report provides the most direct evidence of reactivation Histoplasmosis after anti-TNF therapy. Although the precise mechanisms by which anti-TNF-α therapy causes reactivation of HC need to be investigated, TNF-α seems to be a central mediator of protective immunity in HC infections (see Fig. 1).

References


Figure 1 Proposed mechanism of reactivation reactivation: Anti-TNF-α therapy in Crohn’s disease may lead to an unbiased increase in Th2 cytokines which may reactivate histoplasmosis.


